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Precision medicine and skin cancer therapy: dealing with a moving target

Reinhard Dummer

After years of standstill, there are today new avenues to treat cutaneous malignancies. Intense basic research applying the most advanced technology has resulted in a deep understanding of the molecular biology and the genetic background of basal cell carcinoma (BCC), melanoma and other malignancies.

BCC today is considered as a malignancy that is highly dependent on an activated sonic hedgehog pathway. Most BCCs present inactivating mutations of patch that acts as a tumor suppressor in BCC or activating mutations in smoothened that can be considered as an oncogenic driver in the disease. Mutations in these key players of the hedgehog signaling pathway are involved in more than 90% of all BCCs. Consequently, there was an urgent need for the development of small molecules that interfere with the function of smoothened such as vismodegib or sonidegib and others [1]. As an activated hedgehog pathway appears to be a condition sine qua non in BCC, most tumors have responded with tumor shrinkage during systemic therapy with these inhibitors. However, there are still many open questions about the detailed mechanism of action, the impact of immune responses and the optimal scheduling of these inhibitors. The toxicity profile of these drugs nicely illustrates where hedgehog signaling is still needed in the adult human being. The maintenance and metabolism of muscle cells, the biochemical processes of tasting and the initiation of the hair follicle cycle depend on hedgehog signaling, and consequently are affected during systemic therapy with smoothened inhibitors. The principal open question in this context is: can a systemic therapy with smoothened inhibitors cure advanced or metastatic BCC? This might be possible only in the minority of patients; however, the addition of further treatment modalities and molecules, such as EGF-R-inhibitors, MEK-inhibitors or other treatment modalities including immunotherapy might contribute to increase the cure rate.

In contrast to BCC, which is characterized by an activated hedgehog signaling pathway in most, if not all, cases, melanoma appears to be a very heterogeneous disease. Actually, we shall talk today about the melanomas. We have to distinguish melanomas derived from melanocytes associated with the epidermis from other sites such as ocular origin or dermal origin in the context of congenital nevi [2] or naevus blue. Even in the group of mucosal melanoma there appears to be a difference between mucosal melanoma derived from sinonasal mucosa versus mucosal melanomas derived from genital mucosa. These differences are clinically relevant as the frequency of a c-Kit mutation is much higher in vulvovaginal melanomas in comparison with sinonasal melanoma [3]. Still there is clear evidence that the activation of the MAP-kinase pathway is a key driver in the majority of the melanomas. Activating mutations for BRAF and NRAS are well known genetic causes. Intelligent pharmacology has provided us with a number of specific and potent inhibitors of the kinases BRAF and MEK [4] that play a crucial role in this pathway and additional inhibitors that interfere with ERK or RAS are in preclinical or early clinical development.

The second promising avenue in the development of new therapeutic strategies is immunotherapy. There is a modest activity of interferon alpha in early stages of metastatic melanoma, there are impressive data on the impact of adoptive cell transfer in a selected patient population with metastatic melanoma and now there is the promise of the use of immune check point blocking agents such as ipilimumab, nivolumab and lambrolizumab. Modern vaccines are additional attractive tools in this repertoire [5].

For the first time in dermato-oncology, we have today promising predictive markers for the outcome of a therapy, such as the BRAF mutation for targeted

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therapy using vemurafenib and other BRAF inhibitors and the expression of PD1L for the use of anti-PD1 antibodies in advanced cancers, such as melanoma renal cell cancer and lung cancer. However, very recently we had to experience that these predictive markers are not stable during the course of a malignant disease. The expression of PD1L is affected by interferon gamma secreted by infiltrating CD8 + lymphocytes [6]. In addition, recent investigations also suggest that the percentage of BRAF mutated cells within one melanoma lesion can be reduced during therapy with respective inhibitor and additional tumor clones with other driver mutations can evolve [7].

We must conclude that (skin) cancers are adaptive and moving targets tremendously impacting on the long-term benefit of the new treatment approaches.

We will need to gather all the knowledge from basic research and clinical skills to deal with these challenging circumstances.

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Conflicts of interest

None declared.

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